

prior art methods is the spray-drying step. In the spray-drying step testosterone and/or one or more testosterone ester is mixed with an organic polymer and optionally at least one auxiliary agent (filler, surfactant, etc), the mixture is dissolved in a solvent, such as ethanol, and the solution is spray dried to form an amorphous active ingredient premix in which the active ingredients are embedded in a polymer matrix. Then subsequently the premix can be mixed with other auxiliary ingredients and compressed to form a single layer tablet. Alternatively an adhesive layer mixture can be prepared as well as the active ingredient premix and the two mixtures can be compressed together to form a bi-layer bioadhesive tablet.

Also note that the new main method-of-manufacturing claim 32 is broader than the similar canceled claim 16, which is limited to mixtures of testosterone with at least one testosterone ester. New method-of-manufacturing claim 32 claims methods using an active ingredient premix that includes only testosterone, only a testosterone ester or a mixture of testosterone and one or more testosterone ester. This agrees with the examples in the specification, since the tablet of example 1 includes testosterone as the only active ingredient, the tablet of example 2 includes only an ester of testosterone and the tablet of examples 3 and 4, appropriate mixtures of testosterone with an ester of it. Again the key feature of the method and the bioadhesive tablet prepared by it is not that there is a mixture of testosterone with one or more of its esters. Instead it is that the tablet is prepared with an amorphous active ingredient premix, which is subsequently mixed with auxiliary ingredients and compressed to form the tablet.

According to page 4 of the specification the bioadhesive tablet prepared in this manner provides much greater testosterone ester availability during buccal administration.

New claims 45 to 53 are product-by-process claims for the bioadhesive tablet made by the methods claimed in claims 32 to 44. These claims claim the more effective tablet that provides the better active ingredient levels than the corresponding tablets of the prior art that are made by simple dry mixing followed by compression to form the tablet.

## II. Obviousness Rejection based on Voorspoels, et al, with or without Timpe

It is respectfully submitted that the new method-of-manufacturing claims 32 to 44 are not *prima facie* obvious from Voorspoels, et al, or Voorspoels, et al, in view of Timpe.

Voorspoels, et al, is a technical article reporting measured testosterone blood levels in dogs after administration of testosterone or an ester of testosterone, by means of a buccal bioadhesive tablet. Voorspoels found that administration of testosterone itself by buccal administration is much preferred to oral administration in a tablet, because buccal administration avoids metabolism of testosterone in the liver, which can reduce the level of testosterone by 98 %. The resulting testosterone concentration profiles in the plasma for administration of testosterone and various esters are shown in Fig. 2 and Fig. 3. The level obtained using testosterone itself in the tablet is at least 4 to

10 x greater than using any of the esters.

The method of making the bioadhesive tablets used by Voorspoels is described in the right hand column of p. 1228. The ingredients are merely mixed and compressed on a Korsch compression machine with a 9 mm flat punch. The composition of the tablets used by Voorspoels is shown in Table II on page 1229. The compositions comprise testosterone or a testosterone ester, CARBOPOL®, sodium stearyl fumarate and waxy maize (filler).

Voorspoels, et al, does not *disclose or suggest* a method of making the bioadhesive tablet by first making an amorphous active ingredient premix by spray-drying a solution of a mixture of the active ingredients optionally with an auxiliary agent. Then the premix is compressed together with other auxiliary ingredients to make applicants' claimed bioadhesive tablet.

The spray-drying step is neither disclosed nor suggested by Voorspoels, et al. Voorspoels, et al, is not concerned with manufacturing methods for bioadhesive tablets, but only with making bioadhesive tablets for studying the effects of esterification of the active testosterone ingredient in a program of buccal administration of it. The sixth paragraph on page 4 of applicants' U.S. specification explains that the prior art dry mixing of the ingredients provides a bioadhesive tablet in which testosterone esters are delivered much less effectively than when the bioadhesive tablet is made by spray-drying. The key according to this disclosure in the specification is the production of a premix of the active ingredients in an amorphous state. The esters in their crystalline state are more difficult to absorb.

Voorspoels, et al, do not suggest this spray-drying step, but instead teach against the claimed invention (method of manufacturing) by teaching dry mixing of the ingredients followed by compression in a tablet press.

It is well established by many U. S. Court decisions that to reject a claimed invention under 35 U.S.C. 103 there must be some hint or suggestion in the prior art of the modifications of the disclosure in a prior art reference or references used to reject the claimed invention, which are necessary to arrive at the claimed invention. For example, the Court of Appeals for the Federal Circuit has said:

"Rather, to establish obviousness based on a combination of elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant...Even when obviousness is based on a single reference there must be a showing of a suggestion of motivation to modify the teachings of that reference.." *In re Kotzab*, 55 U.S.P.Q. 2<sup>nd</sup> 1313 (Fed. Cir. 2000). See also M.P.E.P. 2141

Voospoels, et al, do not teach or suggest that the step of making the amorphous active ingredient premix by spray-drying prior to compression with auxiliary substances to make the tablet.

Tablet claims 45 to 53 are product-by-process claims. A Declaration is being prepared based on experimental evidence that shows that the bioadhesive tablets prepared by the manufacturing method according to the claimed invention provide better active ingredient levels during buccal administration.

Features in the dependent method claims should also be considered. For

example, the preferred ratio of testosterone to testosterone ester of claim 35 is not suggested in Voorspoels, et al, for embodiments in which a mixture of testosterone and one of its esters is employed. Voorspoels, et al, does not even disclose or suggest using a mixture of testosterone and one of its esters as the active ingredient mixture. How could this reference suggest the preferred ratios of claim 35?

In addition, the preferred spray during solvent and organic polymer of claims 36 and 37 are not suggested by this reference.

Other features of the dependent method claims are also not suggested by this reference, such as selecting the testosterone ester or esters provided in the mixture according to chain length and steric structure, in order to provided the predetermined testosterone profile.

Timpe does not suggest or disclose the key distinguishing feature of the method of manufacturing according to claim 32, namely the intermediate premix, i.e. the amorphous active ingredient premix made by spray-drying. Examples 1 to 3 in column 6 of Timpe clearly state that the ingredients of the tablets are mixed and molded into tablets in the known way. See also column 4, lines 13 to 22; column 4, lines 50 to 60, which support this conclusion.

Timpe clearly does not suggest the spray-drying feature for making the intermediate active ingredient premix and thus the method claims 32 to 44 are not prima facie obvious from the combination of Voorspoels, et al, and Timpe.

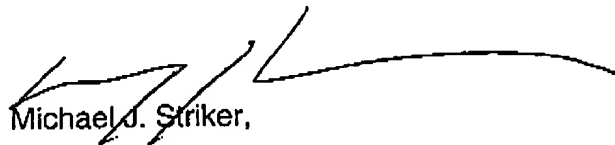
A Declaration will be filed at a later date to show that the tablet claims 45 to 53 claim bioadhesive tablets having unexpectedly better properties than prior art bioadhesive tablets containing testosterone and/or testosterone ester active ingredients or mixtures thereof.

For the foregoing reasons it is respectfully submitted that new claims 32 to 53 should **not** be rejected under 35 U.S.C. 103 (a) as obvious over Voorspoels, et al, or Voorspoels, et al, in view of Timpe.

Should the Examiner require or consider it advisable that the specification, claims and/or drawing be further amended or corrected in formal respects to put this case in condition for final allowance, then it is requested that such amendments or corrections be carried out by Examiner's Amendment and the case passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing the case to allowance, he or she is invited to telephone the undersigned at 1-631-549 4700.

In view of the foregoing, favorable allowance is respectfully solicited.

Respectfully submitted,



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